09/786276/5610

COPY FOR IB

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Artcle 36 and Rule 70)

Applicant's or agent's file reference #138	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. **PCT/KR00/01170**	International filing date *(day/month/year)* 18 OCTOBER 2000 (18.10.2000)	Priority date *(day/month/year)* 18 OCTOBER 1999 (18.10.1999)

International Patent Classification (IPC) or national classification and IPC

IPC7 C07C 67/00, C12P 7/00

Applicant

Samsung Fine Chemicals Co., Ltd. et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demamd	Date of completion of this report
02 MAY 2001 (02.05.2001)	25 JANUARY 2002 (25.01.2002)

Name and mailing address of the IPEA/KR	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 920 Dunsan-dong, Seo-gu, Daejeon Metropolitan City 302-701, Republic of Korea	KANG, Jeon Kwan
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-5553

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR00/01170

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[ ] the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

[ ] the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statment) under Article 19
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

[ ] the drawings:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

[ ] the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language English which is

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[X] the language of publication of the international application(under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide** and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained inthe international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disc losure in the international applicationas as filed has been furinshed.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages _____

[ ] the claims, Nos. _____

[ ] the drawings, sheet _____

5. [ ] This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box(Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed." and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR00/01170

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-9	YES
	Claims		NO
Inventive step (IS)	Claims	1-9	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The invention defined by the claims is a process for preparing a chiral ester(100) by reacting the following materials;

1. a racemic alcohol(4)
2. a ruthenium complex(1,2,3) to activate racemization of said racemic alcohol(4)
3. a lipase to acylate one enantiomer selectively from said racemic alcohol(4)
4. an acyl donor compound to supply acyl group to said lipase

No individual citation or obvious combination of citations discloses this process for preparing a chiral ester(100).

The closest art is EP-A2-375417. Although this is directed to a process for preparing a chiral ester, the method employed is different to the present invention.

Therefore the subject matter of claims 1-9 meets the requirements of Article 33(2)-(4).

09/786276

PCT/KR00/01170

F ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 27 June 2001 (27.06.01)	
International application No. PCT/KR00/01170	**Applicant's or agent's file reference** #138
International filing date (day/month/year) 18 October 2000 (18.10.00)	**Priority date** (day/month/year) 18 October 1999 (18.10.99)
Applicant PARK, Jai, Wook et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 May 2001 (02.05.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PCT/KR00/01190

PCT REQUEST

#138

Original (for **SUBMISSION**) - printed on 18.10.2000 04:15:24 PM

0 0-1	**For receiving Office use only** International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4 0-4-1	**Form - PCT/RO/101 PCT Request** Prepared using	PCT-EASY Version 2.91 (updated 06.12.1999)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Korean Industrial Property Office (RO/KR)
0-7	**Applicant's or agent's file reference**	#138
I	**Title of invention**	PREPARING METHOD OF CHIRAL ESTER
II	**Applicant**	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	Samsung Fine Chemicals Co., Ltd.
II-5	Address:	190, Yeocheon-dong Nam-ku 680-090 Ulsan Republic of Korea
II-6	State of nationality	KR
II-7	State of residence	KR
II-8	Telephone No.	82-2-772-1742
II-9	Facsimile No.	82-2-772-1749
III-1	**Applicant and/or inventor**	
III-1-1	This person is:	applicant only
III-1-2	Applicant for	all designated States except US
III-1-4	Name	Pohang University of Science and Technology
III-1-5	Address:	San 31, Hyoja-dong Nam-ku, Pohang-si 790-784 Kyongsangbuk-do Republic of Korea
III-1-6	State of nationality	KR
III-1-7	State of residence	KR

PCT REQUEST #138

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III-2	**Applicant and/or inventor**	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	PARK, Jai Wook
III-2-5	Address:	6-501, Professor Apt., 756 Jigok-dong, Nam-ku, Pohang-si 790-390 Kyongsangbuk-do Republic of Korea
III-2-6	State of nationality	KR
III-2-7	State of residence	KR
III-3	**Applicant and/or inventor**	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	KIM, Man-Joo
III-3-5	Address:	6-1405, Professor Apt., 756 Jigok-dong, Nam-ku, Pohang-si 790-390 Kyongsangbuk-do Republic of Korea
III-3-6	State of nationality	KR
III-3-7	State of residence	KR
III-4	**Applicant and/or inventor**	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	KOH, Jeong Hwan
III-4-5	Address:	12-213,Pohang University of Science and Technology Dormitory, 756 Jigok-dong, Nam-ku, Pohang-si 790-390 Kyongsangbuk-do Republic of Korea
III-4-6	State of nationality	KR
III-4-7	State of residence	KR
III-5	**Applicant and/or inventor**	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	JUNG, Hyun Min
III-5-5	Address:	3-403, Graduate Apt., 756 Jigok-dong, Nam-ku, Pohang-si 790-390 Kyongsangbuk-do Republic of Korea
III-5-6	State of nationality	KR
III-5-7	State of residence	KR

PCT REQUEST #138

Original (for **SUBMISSION**) - printed on 18.10.2000 04:15:24 PM

IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	HUH, Sang Hoon
IV-1-2	Address:	13th Fl. Hyecheon Bldg, 831, Yeoksam-dong Kangnam-ku 135-792 Seoul Republic of Korea
IV-1-3	Telephone No.	82-2-553-1331
IV-1-4	Facsimile No.	82-2-557-1290
IV-1-5	e-mail	hallalaw@kornet.net
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

PCT REQUEST #138

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V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	**Exclusion(s) from precautionary designations**	NONE	
VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	18 October 1999 (18.10.1999)	
VI-1-2	Number	1999-45040	
VI-1-3	Country	KR	
VII-1	**International Searching Authority Chosen**	Korean Industrial Property Office (KIPO) (ISA/KR)	
VIII	**Check list**	number of sheets	electronic file(s) attached
VIII-1	Request	5	–
VIII-2	Description	16	–
VIII-3	Claims	6	–
VIII-4	Abstract	1	#138.txt
VIII-5	Drawings	0	–
VIII-7	TOTAL	28	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	–
VIII-12	Priority document(s)	Item(s) VI-1	–
VIII-16	PCT-EASY diskette	–	diskette
VIII-18	**Figure of the drawings which should accompany the abstract**		
VIII-19	**Language of filing of the international application**	Korean	
IX-1	**Signature of applicant or agent**		
IX-1-1	Name (LAST, First)	HUH, Sang Hoon	

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	

PCT REQUEST #138

Original (for SUBMISSION) - printed on 18.10.2000 04:15:24 PM

10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/KR
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

HUH, Sang, Hoon
Hyecheon Building
13th Floor
831, Yeoksam-dong
Kangnam-ku
Seoul 135-792
RÉPUBLIQUE DE CORÉE

Date of mailing (day/month/year) 22 November 2000 (22.11.00)	
Applicant's or agent's file reference #138	**IMPORTANT NOTIFICATION**
International application No. PCT/KR00/01170	International filing date (day/month/year) 18 October 2000 (18.10.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 18 October 1999 (18.10.99)
Applicant SAMSUNG FINE CHEMICALS CO., LTD. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
18 Octo 1999 (18.10.99)	1999/45040	KR	14 Nove 2000 (14.11.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Anman QIU

Telephone No. (41-22) 338.83.38

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 April 2001 (26.04.2001)

PCT

(10) International Publication Number
WO 01/28970 A1

(51) International Patent Classification[7]: C07C 67/00, C12P 7/00

(21) International Application Number: PCT/KR00/01170

(22) International Filing Date: 18 October 2000 (18.10.2000)

(25) Filing Language: Korean

(26) Publication Language: English

(30) Priority Data:
1999/45040 18 October 1999 (18.10.1999) KR

(71) Applicants *(for all designated States except US)*: **SAMSUNG FINE CHEMICALS CO., LTD.** [KR/KR]; 190 Yeocheon-dong, Nam-ku, 680-090 Ulsan (KR). **POHANG UNIVERSITY OF SCIENCE AND TECHNOLOGY** [KR/KR]; San 31, Hyoja-dong, Nam-ku, Pohang-si, Kyongsangbuk-do 790-784 (KR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PARK, Jai, Wook** [KR/KR]; 6-501, Professor Apt., 756 Jigok-dong, Nam-ku, Pohang-si, Kyongsangbuk-do 790-390 (KR). **KIM, Mahn-Joo** [KR/KR]; 6-1405, Professor Apt., 756 Jigok-dong, Nam-ku, Pohang-si, Kyongsangbuk-do 790-390 (KR). **KOH, Jeong, Hwan** [KR/KR]; 12-213, Pohang University of Science and Technology Dormitory, 756 Jigok-dong, Nam-ku, Pohang-si, Kyongsangbuk-do 790-390 (KR). **JUNG, Hyun, Min** [KR/KR]; 3-403, Graduate Apt., 756 Jigok-dong, Nam-ku, Pohang-si, Kyongsangbuk-do 790-390 (KR).

(74) Agent: **HUH, Sang, Hoon**; Hyecheon Building, 13th Floor, 831, Yeoksam-dong, Kangnam-ku, Seoul 135-792 (KR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,

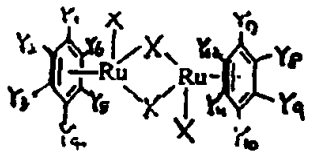
[Continued on next page]

(54) Title: PREPARING METHOD OF CHIRAL ESTER

(1)

(a)

(b)



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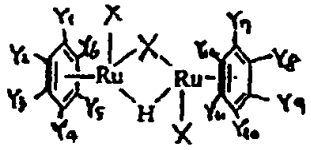
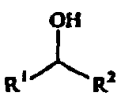
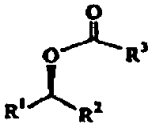


(3)



(4)



(100)

(57) Abstract: The present invention is to provide a process for preparing a chiral ester expressed in formula (100) by reacting; a racemic alochol of formula (4); a ruthenium complex selected from the group consisting of compounds 1,2 and 3 expressed in formulas (1),(2), and (3) to activate racemization of said racemic alchol; a lipase to acylate one enantiomer selectively from said racemic alcohol; and an acyl donor compound to supply acyl group to said lipase, formula (1) wherein Q is (a) or (b); and X is Br, Cl or I; formula (2) wherein Y_1,Y_2,Y_3,Y_4,Y_5,Y_6,Y_7,Y_8,Y_9,Y_{10},Y_{11} and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I; formula (3) wherein Y_1,Y_2,Y_3,Y_4,Y_5,Y_6,Y_7,Y_8,Y_9,Y_{10},Y_{11}, and Y_{12}, are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I; and formulae wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

WO 01/28970 A1

DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *With international search report.*

— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PREPARING METHOD OF CHIRAL ESTER

BACKGROUND OF THE INVENTION

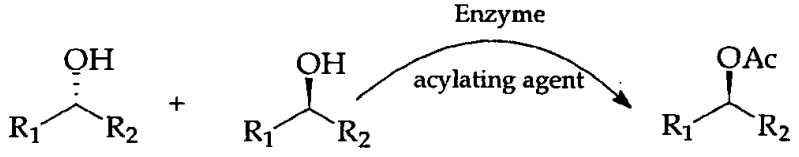
Field of the Invention

The present invention relates to a method for preparing a chiral ester and more particularly, the method for preparing an optically pure chiral ester from a racemic alcohol at a high yield.

Recently, studies for using a metal or an enzyme as a catalyst have been increased in asymmetric syntheses. It has been widely known to use an enzyme as a catalyst for kinetic resolution of a racemic mixture in organic syntheses. A variety of effective methods for hydrolysis of an ester and acylation of an alcohol in the presence of lipase as a catalyst has been reported.

Kinetic resolution is the fact that the two enantiomers react at different rates with a chiral addend. An effective kinetic resolution is the enantioselective conversion from a racemic mixture to an optically pure product as shown in scheme 1, leaving the other enantiomer in a reaction medium.

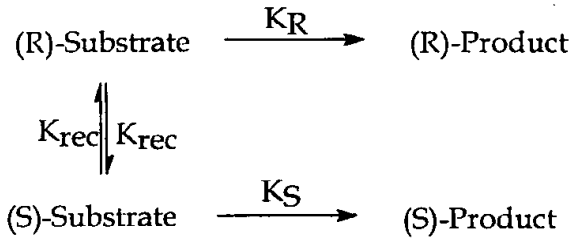
Scheme 1



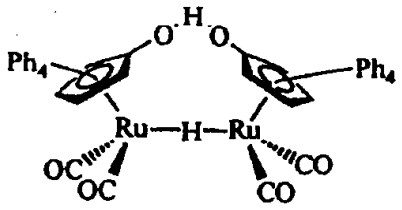
It is well known to prepare a chiral ester from a racemic alcohol by kinetic resolution using esterase. It is possible to obtain an optically pure ester but a maximum yield of this reaction is limited to 50% as shown in scheme 1. Therefore, dynamic kinetic resolution performing kinetic resolution and racemization of an alcohol simultaneously is introduced to resolve such

problems (scheme 2).

Scheme 2



The well-known example of a dynamic kinetic resolution is the reaction by using ruthenium complex expressed in the following structure and lipase (Novozym 435) [B. A. Persson, A. L. E. Larsson, M. L. Ray, and J. E. Backvall, *J. Am. Chem. Soc.* 1999, **121**, 1645].



Because racemization of a starting material is performed simultaneously with kinetic resolution, the effectiveness of the starting material is very high and thus, yield of obtaining (R) or (S) enantiomer is theoretically 100%. However, even if the optical purity of a chiral ester obtained by dynamic kinetic resolution is 99 e. e.%, 12 to 40% of ketone as a by-product is produced.

SUMMERY OF THE INVENTION

Therefore, an object of the present invention is to provide a process for preparing an optically pure chiral ester from a racemic alcohol by dynamic kinetic resolution with minimum production of a ketone.

Detailed Description of the Invention

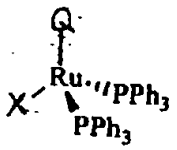
A process for preparing a chiral ester of the present invention is characterized by reacting:

a racemic alcohol;

a ruthenium complex selected from the group consisting of compounds 1, 2 and 3 expressed in formulas 1 to 3 to activate racemization of said racemic alcohol;

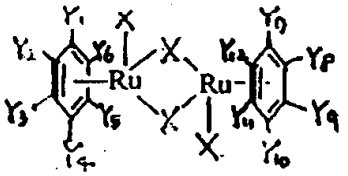
a lipase to acylate selectively one of enantiomers of said racemic alcohol; and

an acyl donor group to supply acyl group to said lipase,



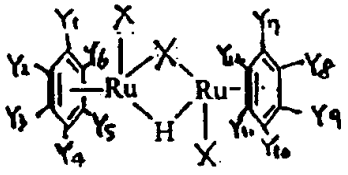
(1)

wherein Q is  or  ; and X is Br, Cl or I;



(2)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;

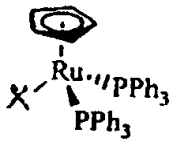


(3)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a

hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I.

Said ruthenium complex is selected from the group consisting of the compounds 5 to 12 expressed in the following formulas 5 to 12,



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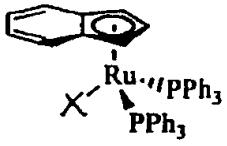

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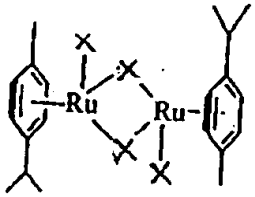

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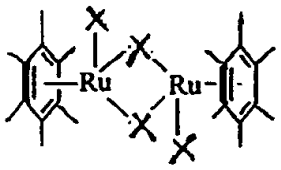

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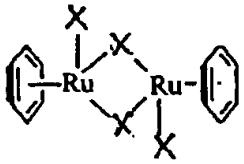

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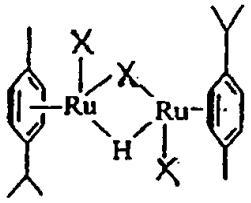

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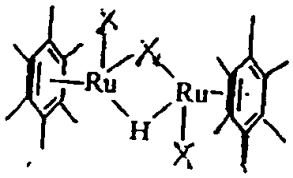

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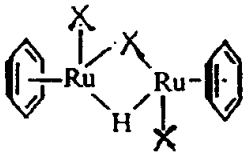


(12)

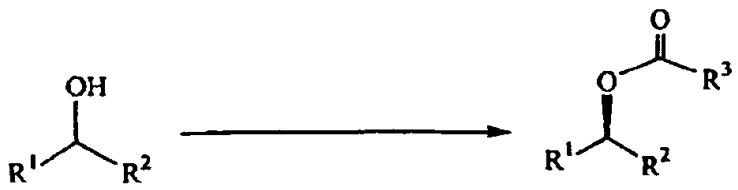
wherein X is Cl, Br or I, the most preferably Cl.

Preferred content of ruthenium complex is 0.1 to 5 mol%, relative to a racemic alcohol. If the content is more than 5 mol%, cost becomes expensive. On the other hand, if it is less than 0.1 mol%, the rate of the reaction becomes too slow.

A method for preparing a chiral ester from a racemic alcohol by dynamic kinetic resolution is described in detail as set forth hereunder.

A mixture of a racemic alcohol, ruthenium complex selected from compounds 1, 2 and 3, lipase and an acyl donor compound is reacted in a solvent in the presence of a base shown in Scheme 3,

Scheme 3



(4) (100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

A reaction condition varies with a structure of ruthenium complex. When the ruthenium complex of formula 6 is used, an oxygen gas is required essentially in the reaction and it is performed at a temperature of 40 to 60℃. Said oxygen gas reacts with phosphine, which is a ligand bonded with ruthenium, to convert to phosphine oxide. When the ruthenium complex of formula 7 is used, the reaction is performed at a temperature of 20 to 40℃. When the ruthenium complex of formula 10 is used, the reaction is performed at a temperature of 20 to 40℃. A base is also required to remove acid generated during the reaction. Said base includes triethylamine or diisopropylethyl amine but it is not limited to these examples.

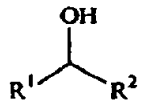
The ruthenium complex of formula 7 is commercially available and is converted to the ruthenium complex of formula 10 in alcohol/base condition. Therefore, results from the ruthenium complex of formula 7 and the ruthenium complex of formula 10 are almost same.

A mechanism of a reaction of a racemic alcohol, ruthenium complex selected from compounds 1, 2 and 3, lipase and an acyl donor compound is described in detail hereunder.

An acyl group supplied from the acyl donor compound is reacted with lipase and this lipase is further reacted with one enantiomer of a racemic alcohol selectively to produce a chiral ester. The other enantiomer is racemized by reacting with ruthenium complex. And further one enantiomer from this racemic alcohol is acylated selectively by lipase and this reaction is repeated to produce optically pure chiral ester with preventing generation of ketone which is a by-product in conventional dynamic kinetic resolution.

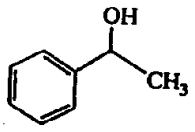
Reaction solvent is not limited but it is preferred to use methylene chloride, toluene, benzene, or hexane because a solvent commonly affects production yield in enzymatic catalysis reaction. An amount of said solvent is used to be 0.2 to 0.3 M concentration of a racemic alcohol.

Said racemic alcohol is generally expressed in the formula 4. It is not limited but examples of the present invention are the following compounds 4a, 4b, 4c, 4d, 4e or 4f,

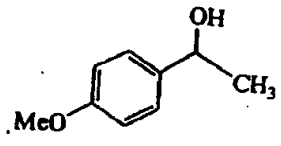


(4)

wherein R^1 and R^2 are the same as defined above.



(4a)



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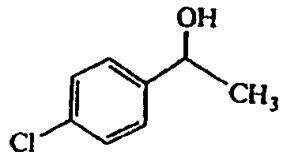

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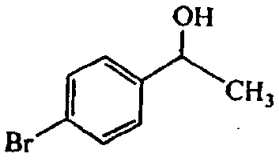

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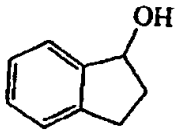

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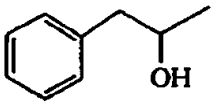


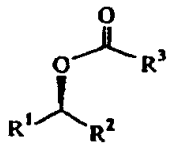
(4f)

Said lipase, which is esterase, acylates one enantiomer from a racemic alcohol selectively to a chiral ester. Examples of lipase are *Pseudomonas cepacias* lipase and *Candida antarctica* lipase and more particulary, *Candida antarctica* component B lipase supported on acrylic resin (Novozym 435, Novo company) or *Pseudomonas cepacias* lipase supported on ceramic particle (lipase PS-C, Amano company). An amount of said lipase is in the range of 10 to 60mg, preferably 30 mg, relative to 1 mmol of an alcohol in Novozym 435 case, and is in the range of 50 to 320 mg, preferably 160 mg, relative to 1 mmol of an alcohol in lipase PS-C case.

Said acyl donor supplies an acyl group to a lipase and acts to move a reaction balance to an acylated product in the presence of a lipase. Preferred acyl donor is aryl ester or alkenyl acetate, the most preferably aryl ester such as

p-chlorophenyl acetate having electron withdrawing group. An example of alkenyl acetate is isoprophenyl acetate. Such acyl donor compounds are preferred to use because they have an appropriate reactivity without inhibiting racemization. A preferred amount of said acyl donor compound is 2 to 4 equivalents to 1 equivalent of racemic alcohol. If the amount is more than 4 equivalents to 1 equivalent of racemic alcohol, it is difficult to isolate after a reaction. On the other hand, if it is less than 2 equivalents to 1 equivalent of racemic alcohol, the rate of acylation becomes too slow.

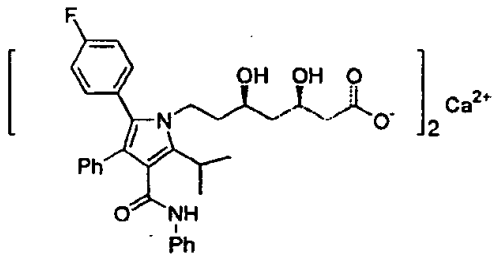
A chiral ester expressed in formula 100 is obtained by reacting a racemic alcohol, a ruthenium complex, a lipase, and an acyl donor compound,



(100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

The chiral ester of formula 100 of the present invention can be used as a synthetic intermediate for preparing various chiral compounds, chiral pharmaceutical drugs or chiral agrochemicals and more particularly, used as an essential intermediate for preparing Atorvastatin expressed in formula 101 which is a useful drug for treatment for hyperlipemia, L-Carnitine expressed in formula 102 which is as an additive used in food and drugs, and Agenerase expressed in formula 103 which is an essential intermediate of AIDS drug.



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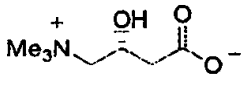

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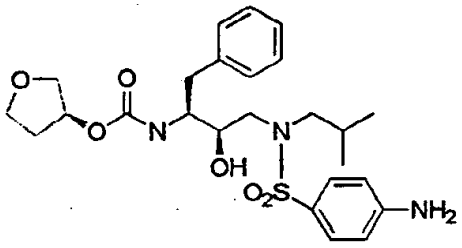
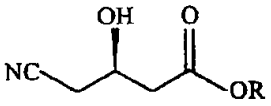


(103)

Especially, a chiral compound of formula 100a which is one of the compounds of the present invention is a key intermediate for preparing Atorvastatin of formula 101 disclosed in US Patent No. 5,908,953,



(100a)

wherein R is a low alkyl group.

The process for preparing a chiral ester of formula 100 of the present invention provides minimum production of by-products such as unreacted alcohol residue up to less than 10% and maximum production of product up to 98% having a high optical purity of 99% or more. Because optical purity is the most important factor in preparing chiral compounds for food and pharmaceutical drugs, the chiral ester of the present invention can be used as a useful starting material in various fields, especially fine chemical field.

The following examples are intended to be illustrative of the present invention and should not be construed as limiting the scope of this invention defined by the appended claims.

Example 1

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.75mmol), ruthenium complex of formula 6(0.0130mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 2.0ml of dichloromethane to give a redish brown suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition. Oxygen(0.0130mmol) was injected with syringe in the reaction suspension and then it was heated at 60℃ for 43 hours.

Examples 2-6

The product, a chiral ester, was prepared by the same procedure of Example 1 except to use racemic alcohol of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Example 7

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.25mmol), ruthenium complex of formula 7(0.0130mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 1.2ml of methylene chloride to give a dark redish suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition and then it was heated at 40℃ for 44 hours.

Examples 8-12

The product, chiral ester, was prepared by the same procedure of Example 6 except to use racemic alcohols of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Example 13

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.25mmol), ruthenium complex of formula 10(0.0100mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 1.2ml of methylene chloride to give a dark redish suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition and then it was heated at 40℃ for 44 hours.

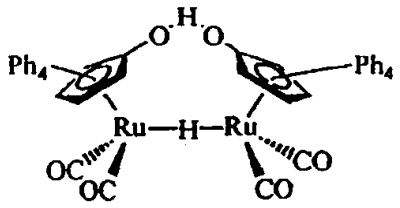
Examples 14-18

The product, chiral ester, was prepared by the same procedure of Example 11 except to use a racemic alcohol of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Comparative Example 1

A racemic alcohol of formula 4a(2mmol), ruthenium complex expressed in the following structure below(0.04mmol), 60mg of Novozym 435, and *p*-chlorophenyl acetate(6mmol) were mixed in 5ml of toluene to give a dark redish suspension.

The reaction suspension was heated at 70℃ for 46 hours under argon gas.



Comparative Examples 2-5

The product, a chiral ester, was prepared by the same procedure of Comparative Example 1 except to use racemic alcohols of formulas 4b, 4d, and 4e and octan-2-ol instead of a racemic alcohol of formula 4a.

Yield, optical purity, and formation of ketone of each reaction of Examples 1-15 and Comparative Examples 1-5 were determined and tabled in Table 1. Said yield was analyzed by ^{1}H-NMR spectrum, and said optical purity was determined by high performance liquid chromatography. Said ^{1}H-NMR spectrum was taken by using Bruker AM 300 and said high performance liquid chromatography was SpectraSystem P2000.

Table 1

Section	Formation of ketone (%)	Yield (%)	Optical purity (e.e.%)
Example 1	0	85	96
Example 2	0	82	99
Example 3	0	98	99
Example 4	0	91	95
Example 5	0	85	97
Example 6	0	92	96
Example 7	8	90	94
Example 8	10	90	99
Example 9	8	90	99

Example 10	8	92	99
Example 11	8	83	99
Example 12	7	91	98
Example 13	5	95	94
Example 14	7	93	99
Example 15	5	93	97
Example 16	4	96	99
Example 17	4	85	99
Example 18	4	95	99
Comp. Example 1	20	Below 80	-
Comp. Example 2	40	Below 60	-
Comp. Example 3	22	Below 78	-
Comp. Example 4	23	Below 77	-
Comp. Example 5	20	Below 80	-

As shown in Table 1, the amount of a ketone formed as a by-product in Comparative Examples 1 to 5 is in the range of 20 to 40% while that in Examples 1 to 18 is less than 10%. Therefore, the yield of the final product, a chiral ester, prepared by Examples 1 to 18 is much more improved.

As a result, it is proved that the present invention provides a process for preparing an optically pure chiral ester from a racemic alcohol with minimizing the formation of ketone at a high yield in the presence of catalysts which are ruthenium complex selected from formulas 1, 2, and 3, and lipase.

CLAIMS

What is claimed is :

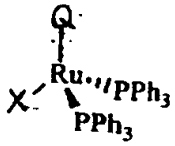
1. A process for preparing a chiral ester expressed in formula 100 by reacting;

a racemic alcohol of formula 4;

a ruthenium complex selected from the group consisting of compounds 1, 2, and 3 expressed in formulas 1, 2, and 3 to activate racemization of said racemic alcohol;

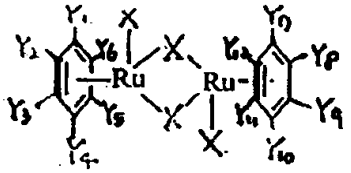
a lipase to acylate one enantiomer selectively from said racemic alcohol; and

an acyl donor compound to supply acyl group to said lipase,



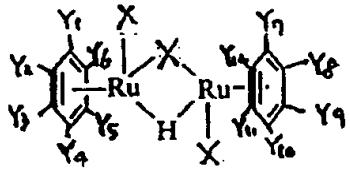
(1)

wherein Q is  or  ; and X is Br, Cl or I;



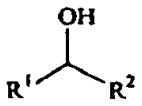
(2)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;



(3)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I; and



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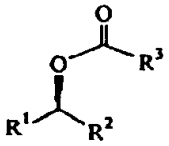
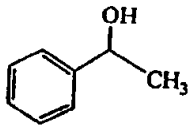


(100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

2. The process for preparing a chiral ester according to claim 1, wherein said racemic alcohol is selected from the group consisting of the compounds 4a, 4b, 4c, 4d, 4e and 4f.



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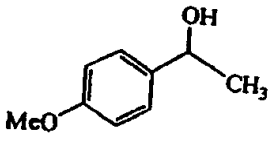

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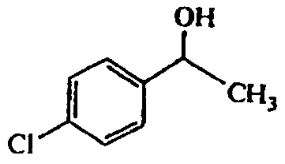
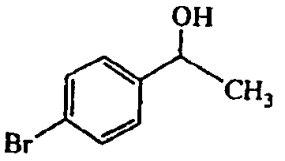
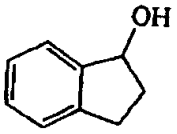


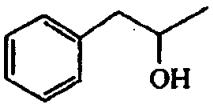
(4c)



(4d)



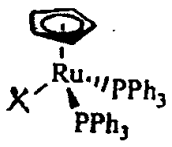
(4e)



(4f)

3. The process for preparing a chiral ester according to claim 1, wherein said lipase is selected from the group consisting of *Pseudomonas cepacias* lipase and *Candida antarctica* lipase.

4. The process for preparing a chiral ester according to claim 1, wherein said ruthenium complex is selected from the group consisting of compounds 5, 6, 7, 8, 9, 10, 11 and 12,



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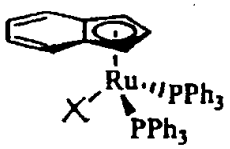

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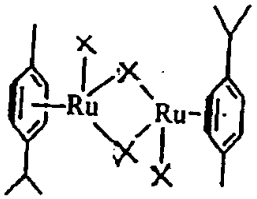

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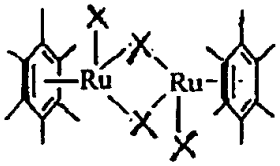

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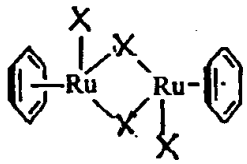
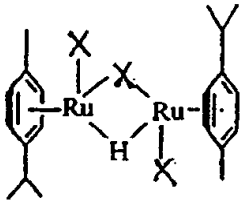
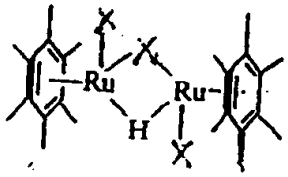


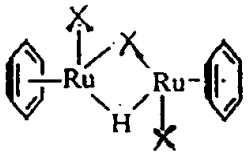
(9)



(10)



(11)



(12)

wherein X is Cl, Br or I, the most preferably Cl.

5. The process for preparing a chiral ester according to claim 3, wherein X is Cl.

6. The process for preparing a chiral ester according to claim 1, wherein said reaction requires use of oxygen gas.

7. The process for preparing a chiral ester according to claim 1, wherein a content of said ruthenium complex or its derivatives is in the range of 0.1 to 5mol% to said racemic alcohol.

8. The process for preparing a chiral ester according to claim 1, wherein said acyl donor compound is aryl ester.

9. The process for preparing a chiral ester according to claim 7, wherein said aryl ester is selected from the group consisting of *p*-chlorophenyl acetate and alkenyl acetate.

INTERNATIONAL SEARCH REPORT

international application No.
PCT/KR00/01170

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07C 67/00, C12P 7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)
C07C, C12P

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)
STN(REGISTRY, CAPLUS)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T,A	Novel synthetic routes to several new, differentially substituted ruthenium tris(4,4'-disubstituted-2,2-bipyridine) complexes, Dusan Hsek et al, page 308-316, American Chemical Society (2000), 39(2) see the scheme 1 and table 1	1-9
T,A	Catalytic asymmetric and chemoselective aerobic oxidation : kinetic resolution of sec-alcohols, Masutani K. et al, page 5119-5123, Tetrahedron letters (2000) 41(26) see the page 5120(reaction, scheme) and table 1	1-9
T,A	synthesis of ruthenium complexes with planar-chiral cyclopentadienyl-pyridine or -phosphine bidentate ligands, Noriko Dodo et al, page 35-41, Dalton (2000) 1, Royal Society of chemistry see the scheme 2 and 5	1-9
A	EP-A2-375417 see the whole document	1-9
P,A	EP-A1-992481 see the whole document	1-9
A	Ruthenium(2)-catalyzed asymmetric transfer hydorgenation of ketones using a formic acid-triethylamine mixture, Fujii, Akio et al, page 2521-2, American Chemical Society (1996),	1-9

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevence
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 FEBRUARY 2001 (09.02.2001)	12 FEBRUARY 2001 (12.02.2001)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR00/01170

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2-375417	1990.6.27	JP-A2-02-169555	1990.6.29
EP-A1-992481	2000.4.12	DE-A1-1998-5517	2000.4.6
		JP-A2-2000-119217	2000.4.25

----------End of documents----------

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2001

Ferrocyanide. [13601-19-9] Tetrasodium ...ate(4−); sodium hexacyanoferrate(II); ...la; sodium prussiate yellow. $C_6FeN_6Na_4$ ... 3.71%, Fe 18.38%, N 27.65%, Na 30.26% ... w of properties, chemistry and synthesis ...*rrocyanides*, American Cyanamid Co. (Bo... k, 1953) 112 pp.

...ale yellow, monoclinic, slightly efflorescent ...ydration occurs >50°. Becomes anhydr... ...rming sodium cyanide, iron, carbon, and ...ater at 1°: 10.2% (calcd as the anhydr salt) ...5°: 17.6%; at 53°: 28.1%; at 85°: 39%; ...tically insol in most organic solvents. ...t mix with hot or concd acids and do not ...light for any length of time to avoid gener... ...yanide. Waste ferrocyanides in streams and ...ceed 2 ppm because irradiated solns become ... Burdick, M. Lipscheutz, *C.A.* **44**, 10939 ...because of strong chemical bondage between ...and the iron, ferrocyanides have a low order ...

...f sodium ferrocyanide solns to slightly acidic ... causes precipitation of insol Prussian blue ...e), $Fe_4[Fe(CN)_6]_3$. Alkaline solns yield sol... ...e[Fe(CN)$_6$]. Sodium ferrocyanide forms gl... in general. Used in ore flotation. In photog... g, toning, and fixing. To prevent caking of ... Additive to pickling baths. Peptizing agent ...abilizer in welding rod coatings. Emulsi... ...alyst.

...n Fluoborate. [13755-29-8] Sodium tetra... ...um borofluoride. BF_4Na; mol wt 109.79. ... Na 20.94%. $NaBF_4$. Prepd according to the ... + 8HF + Na_2CO_3 → $2NaBF_4$ + $7H_2O$ ...-Dörfurt, Z. *Anorg. Allgem. Chem.* **159**, 197 ...n *Handbook of Preparative Inorganic Chem...* ...rauer, Ed. (Academic Press, New York, 2n...

...stout rectangular prisms d^{20} 2.47. mp 38... Does not etch glass when absolutely dry ...00 ml): 108 (26°); 210 (100°). Sparingly sol... ...lns have a bitter taste and are acid to litmus ...ing agent, *see* Lawton, Levy, *J. Am. Chem.* ...55).

...m Fluoride. [7681-49-4] Chemifluor; Duc... ...uoros; Flura-Drops; Karidium; Lemoflur; Lu... Ossin; Osteo-F; Osteofluor; Slow-Fluor; ...afluor. FNa; mol wt 41.99. F 45.25%. ... repd by fusing cryolite with NaOH; by addi... f NaOH or Na_2CO_3 to 40% HF (precipitat... and crystal size depends on pH, but too m... n bifluoride, $NaHF_2$): Müller, *Chem.-Ztg.* ...nik in *Handbook of Preparative Inorg...* ..., G. Brauer, Ed. (Academic Press, New Yo...) 235-236. Technical grades are 90% and 98... ...i in/lb) and dense (23 cu in/lb), and 98% ...ainly sodium and aluminum fluosilicates. ... ...so *et al., Handb. Exp. Pharmakol.* XX (Part ...Springer, Berlin, 1970) pp 144-165. Toxi... *al., Am. Ind. Hyg. Assoc. J.* **30**, 470 (19... studies: J. R. Bucher *et al., Int. J. Cancer* ...iew of toxicology: D. W. Banting, *J. Am. D...* ...91 (1991). Review of clinical efficacy in ... ...l caries: L. G. Petersson, *Caries Res.* **27**, S... ...); of clinical experience in osteoporosis: ... B. Mendlovic, *Endocr. Rev.* **14**, 312...

...gonal crystals (NaCl lattice). d 2.78. mp 99... ...*nous!* Soly in water (g/100 ml): 4.0 (15°... ...). Insol in alc. Aq solns have an alkaline ...partial hydrolysis. pH of freshly prepd soln ...tch glass, but the dry crystals or powder may ...ttles. Sodium fluoride sold as household ... ...inted Nile Blue. LD_{50} orally in rats: 0.18...

Caution: Potential symptoms of overexposure by ingestion are salty or soapy taste; salivation, nausea, abdominal pain, vomiting, diarrhea; dehydration, thirst; sweating; stiff spine; muscle weakness, tremors; CNS depression; shock; arrhythmia. Direct contact may cause dermatitis; irritation of eyes, respiratory system. Potential symptoms of chronic ingestion are mottling of tooth enamel; osteosclerosis, calcification of ligaments of ribs, pelvis. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 282; *Clinical Toxicology of Commercial Products*, R. E. Gosselin *et al.*, Eds. (Williams & Wilkins, Baltimore, 5th ed., 1984) Section III, pp 185-193.

USE: As insecticide, particularly for roaches and ants; in other pesticide formulations; constituent of vitreous enamel and glass mixes; as a steel degassing agent; in electroplating; in fluxes; in heat-treating salt compositions; in the fluoridation of drinking water; for disinfecting fermentation apparatus in breweries and distilleries; preserving wood, pastes and mucilage; manuf of coated paper; frosting glass; in removal of HF from exhaust gases to reduce air pollution. Dental caries prophylactic.

THERAP CAT: In treatment of osteoporosis.

THERAP CAT (VET): Anthelmintic, pediculicide, acaricide.

8692. Sodium Folate. [6484-89-5] Folic acid sodium salt; sodium pteroylglutamate; sodium Folvite. $C_{19}H_{18}N_7NaO_6$; mol wt 463.38. C 49.25%, H 3.92%, N 21.16%, Na 4.96%, O 20.72%. Sold only as sterile soln in ampuls.

Clear, mobile liquid. Yellow to orange-yellow color. pH between 8.5 and 11.0. For spectrophotometric data *see* Folic Acid.

THERAP CAT: Water-soluble hematopoietic vitamin.

8693. Sodium Formaldehydesulfoxylate. [149-44-0] Hydroxymethanesulfinic acid sodium salt; formaldehyde sodium sulfoxylate; formaldehydesulfoxylic acid sodium salt; sodium hydroxymethanesulfinate; sodium methanalsulfoxylate; Aldanil; Rongalite; Rongalite C. CH_3NaO_3S; mol wt 118.09. C 10.17%, H 2.56%, Na 19.47%, O 40.64%, S 27.15%. $Na[HOCH_2SO_2]$. Prepn: Heyl, Greer, *Am. J. Pharm.* **94**, 80 (1922); Binns, **US 2013125** (1935 to Virginia Smelting); Postnikov, Kunin, *J. Appl. Chem. USSR* **13**, 185 (1940). Structure of dihydrate: Truter, *J. Chem. Soc.* **1955**, 3064; **1962**, 3400. Of limited value in treatment of mercuric chloride poisoning: Modell *et al., J. Pharmacol. Exp. Ther.* **61**, 66 (1937).

Dihydrate. Crystals, mp 63-64°, dec at higher temp. Odorless when freshly prepd, but quickly develops a characteristic (garlic) odor. Freely sol in water; practically insol in abs alcohol, ether, benzene. Readily dec by dil acids. Aq soln is practically neutral. *Keep well closed in a cool place.* LD s.c. in mice, 10 g/kg: Rosenthal, *Public Health Rept. (U.S.)* **49**, 908 (1934).

USE: In vat color printing pastes: Borstelmann, Fordemwalt, **US 2597281** (1952 to Am. Cyanamid). In polymerization of ethylenic compds: **GB 816252**; **GB 852593** (1959 to Hercules Powder; 1960 to Air Reduction). In manuf of arsphenamines: Krumwiede, *J. Am. Pharm. Assoc.* **8**, 795 (1919); Heyl, Miller, *Ibid.* **11**, 432 (1922).

THERAP CAT: Treatment of mercury poisoning.

8694. Sodium Formate. [141-53-7] $CHNaO_2$; mol wt 68.01. C 17.66%, H 1.48%, Na 33.80%, O 47.05%. HCOONa.

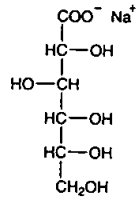
White, deliquesc granules or cryst powder; slight odor of formic acid. d 1.92. mp 253°; at higher temp dec into sodium oxalate and hydrogen, then into sodium carbonate. Sol in ~1.3 parts water; sol in glycerol, slightly in alcohol. The aq soln is neutral, pH ~7. Has buffering action. *Keep well closed.*

USE: In dyeing and printing fabrics; also in anal. chemistry as precipitant for the "noble" metals. Solubilizes trivalent metal ions in soln by forming complex ions. Buffering action resists the pH of strong mineral acids to higher values.

THERAP CAT: Caustic, astringent.

8695. Sodium Gluconate. [527-07-1] Gluconic acid sodium salt. $C_6H_{11}NaO_7$; mol wt 218.14. C 33.04%, H 5.08%, Na 10.54%, O 51.34%. The normal sodium salt of gluconic acid.

Crystals. The technical grade may have a pleasant odor. Soly in water at 25°: 59 g/100 ml. Sparingly sol in alcohol. Insol in ether. Aq solns are stable to short boiling periods.



USE: As sequestering agent forming water-sol complexes with calcium in alkaline media and with iron in near neutral solns. Used in metal plating, mineral tanning of hides, mordanting fabrics, and in water-paste paints. Has been suggested as a photographic processing aid.

8696. Sodium Glycerophosphate. [1334-74-3] 1,2,3-Propanetriol mono(dihydrogen phosphate) disodium salt. $C_3H_7Na_2O_6P$; mol wt 216.04. C 16.68%, H 3.27%, Na 21.28%, O 44.43%, P 14.34%. Three isomers exist: The β-glycerophosphoric acid disodium salt ($(HOCH_2)_2CHOPO_3Na_2$) and D(+)- and L(−)-α-glycerophosphoric acid disodium salt ($HOCH_2CH(OH)CH_2OPO_3Na_2$). Prepn: H. King, F. L. Pyman, *Pharm. J.* **92**, 511 (1914). Exptl use in diagnosis of prostatic carcinoma: M. K. Schwartz *et al., Ann. N.Y. Acad. Sci.* **166**, 775 (1969). Chronic toxicity study of β-form: K. L. Raheja *et al., Toxicology* **8**, 115 (1977). Efficacy of β-form as cariostatic agent: T. H. Grenby, J. M. Bull. *Arch. Oral Biol.* **20**, 717 (1975). GC determn: Y. Handa *et al., J. Chromatog.* **206**, 387 (1981).

β-Form hemiundecahydrate. White, odorless, scale-like crystals; dec >130°. Sol in ~1.5 parts water; more sol in hot water. (pH of aq soln: ~9.5). Insol in alcohol.

THERAP CAT: Tonic.

THERAP CAT (VET): Has been used as a tonic.

8697. Sodium Hexachloroplatinate(IV). [16923-58-3] Disodium hexachloroplatinate(2−); sodium platinichloride; sodium chloroplatinate. Cl_6Na_2Pt; mol wt 453.78. Cl 46.88%, Na 10.13%, Pt 42.99%. $Na_2[PtCl_6]$. Prepn: Grube in *Handbook of Preparative Inorganic Chemistry* **vol. 2**, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1965) pp 1571-1572; Cox, Peters, *Inorg. Syn.* **13**, 173 (1971).

Yellow, hygroscopic crystals. Easily forms hexahydrate at 25° and relative humidity >50% (reconverted to anhydr salt by heat at 110° for one hour). uv max (1 formal HCl): 262 nm (ε 24500). Sol in water, alcohol.

USE: Catalyst.

8698. Sodium Hexafluorosilicate. [16893-85-9] Sodium fluosilicate; sodium silicofluoride; Salufer. F_6Na_2Si; mol wt 188.06. F 60.61%, Na 24.45%, Si 14.93%. Na_2SiF_6. Toxicity study: C. W. Muehlberger, *J. Pharmacol. Exp. Ther.* **39**, 246 (1930). Review of toxicology of fluoride compounds: G. L. Waldbott, *Acta Med. Scand. Suppl.* **400**, 1-44 (1963).

White, granular powder. d 2.68. Melts at red heat with decompn. Sol in 150 parts cold, 40 parts boiling water. Insol in alc. The soln in cold water is neutral. LD in rabbits (mg F/kg): 76 intragastric; in rats (mg F/kg): 42 s.c. (Muehlberger). LD in guinea pigs (mg/kg): 250 orally, 500 s.c. (Waldbott).

USE: In enamels for china and porcelain; manuf opal glass; as insecticide, rodenticide; mothproofing of woolens. Fluoridating agent for drinking water. Intermediate in prodn of synthetic cryolite.

THERAP CAT (VET): Pediculicide.

8699. Sodium Hydride. [7646-69-7] HNa; mol wt 24.00. H 4.20%, Na 95.79%. NaH. Prepd by passing hydrogen into molten sodium dispersed in oil or mixed with a catalyst such as anthracene above 250°: Hansley, Carlisle, *Chem. & Eng. News* **23**, 1332 (1945). Laboratory procedure by hydrogenating sodium dispersions: Mattson, Whaley, *Inorg. Syn.* **5**, 10 (1957). Book: J. Plesek, S. Hermanek, *Sodium Hydride, Its Use in the Laboratory and in Technology* (Iliffe Books, London, 1968) 185 pp.

Silvery needles; the commercial product is a gray-white powder. d 1.396. Dec 425°. Reacts explosively with water, vio-

lently with lower alcohols, ignites spontaneously on standing in moist air. Sol in molten sodium hydroxide, insol in liq ammonia but forms sodamide at moderate temps.

USE: At low temps where reducing properties of sodium are undesirable as in the condensation of ketones and aldehydes with acid esters; in soln with molten sodium hydroxide for the reduction of oxide scale on metals; at high temps as a reducing agent and reduction catalyst.

8700. Sodium Hydrosulfite. [7775-14-6] Sodium sulfoxylate; sodium dithionite. $Na_2O_4S_2$; mol wt 174.11. Na 26.41%, O 36.76%, S 36.83%. $Na_2S_2O_4$. The hydrosulfite of commerce contains 85-90% $Na_2S_2O_4$.

White or grayish-white, cryst powder; slight characteristic odor. Oxidizes in air (more readily so in presence of moisture or when in soln) to bisulfite and bisulfate and acquires an acid reaction. Very sol in water, slightly in alcohol.

Note: The name sodium hydrosulfite is applied also to $NaHSO_2$, mol wt 88.06, sol in water, alcohol. Still more confusion results when "sodium hyposulfite" is applied to this compd ($Na_2S_2O_4$) *see* 1957 Subject Index to *Chem. Abstracts*, p 2218s *under* sodium dithionite.

USE: As reducing agent, particularly in dyeing with indigo and vat dyes; bleaching soaps, straw; removing dyes from dyed fabrics.

8701. Sodium Hydroxide. [1310-73-2] Caustic soda; soda lye; sodium hydrate. HNaO; mol wt 40.00. H 2.52%, Na 57.47%, O 40.00%. NaOH. By reacting calcium hydroxide with sodium carbonate; from sodium chloride by electrolysis; from sodium metal and water vapor at low temp. Description of industrial processes: *Faith, Keyes & Clark's Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 737-745. Toxicity: Fazekas, *Arch. Exp. Pathol. Pharmakol.* **184,** 587 (1937).

Fused solid with crystalline fracture. Rapidly absorbs carbon dioxide and water from the air. Very corrosive (caustic) to animal and vegetable tissue and to aluminum metal in the presence of moisture. Sold as lumps, sticks, pellets, chips, etc. When kept in tight containers, the usual grades contain 97-98% NaOH. mp 318°. d^{25} 2.13. One gram dissolves in 0.9 ml water, 0.3 ml boiling water, 7.2 ml abs alcohol, 4.2 ml methanol, also sol in glycerol. Generates considerable heat while dissolving, or when the soln is mixed with an acid. Volumetric NaOH solns used in the laboratory must be protected from air to avoid formation of carbonate. Concentrated NaOH solns dissolve practically no sodium carbonate. The pH of a 0.05% w/w soln ~12, of a 0.5% soln ~13, of a 5% soln ~14. Density, boiling and freezing pt data for (w/w) water solns. $d_4^{15.5}$: 5% 1.056, 10% 1.111, 20% 1.222, 30% 1.333, 40% 1.434, 50% 1.530. bp: 5% 102°, 10% 105°, 20% 110°, 30% 115°, 40% 125°, 50% 140°. fp: 5% −4°, 10% −10°, 20% −26°, 30% 1°, 40% 15°, 50% 12°. LD orally in rabbits: 500 mg/kg (10% soln) (Fazekas).

Caution: Potential symptoms of overexposure are irritation of eyes, skin and mucous membranes; pneumonitis; eye and skin burns; temporary loss of hair. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-1140, 1997) p 284.

USE: NaOH solutions are used to neutralize acids and make sodium salts, *e.g.*, in petroleum refining to remove sulfuric and organic acids; to treat cellulose in making viscose rayon and cellophane; in reclaiming rubber to dissolve out the fabric; in making plastics to dissolve casein. NaOH solns hydrolyze fats and form soaps; they precipitate alkaloids (bases) and most metals (as hydroxides) from water solns of their salts. Pharmaceutic aid (alkalizer).

THERAP CAT (VET): Caustic; dehorning of calves.

8702. Sodium Hypochlorite. [7681-52-9] ClNaO; mol wt 74.44. Cl 47.63%, Na 30.88%, O 21.49%. NaClO. Strong oxidizing and hydrolyzing agent; used in aqueous solutions of various strengths for its bactericidal properties. Prepn as the pentahydrate from NaOH and Cl_2 in the presence of water: Sanfourche, Gardent, *Bull. Soc. Chim.* [4] **35,** 1089 (1924); Schmeisser in *Handbook of Preparative Inorganic Chemistry* vol. 1, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) pp 309-310. Review of prepn and uses of ***Dakin's solution***, a diluted antiseptic formulation: H. Plagge, *Pharm. Zig.* **138,** No. 14, 26-31 (1993). Review of toxicology and use as household bleach: F. Racioppi *et al., Food Chem. Toxicol.* **32,** 845-861 (1994); of use in health care facilities: W. A. Rutala, D. J. Weber, *Clin. Microbiol. Rev.* **10,** 597-610 (1997). Review of use as endodontic irrigant: R. M. Clarkson, A. J. Moule, *Aust. Dent. J.* **43,** 250-256 (1998).

Prepd as the pentahydrate, crystals, mp 18°. Dec by CO_2 from air. Anhydr NaClO may be obtained by freeze-drying in a vacuum (over concd H_2SO_4). *Anhydr NaClO is very explosive.* Soly at 0°: 29.3 g/100 ml H_2O. Aqueous solutions for household bleach contain ~5.25%. Solutions for use as antiseptics contain ~0.5% sodium hypochlorite and are buffered or stabilized with various agents.

Caution: Potential symptoms of overexposure by ingestion are pain and inflammation of the mouth, pharynx, esophagus, stomach; vomiting; circulatory collapse, cold and clammy skin, cyanosis, shallow respirations; confusion, delirium, coma; edema of pharynx, larynx, glottis with stridor and obstruction; perforation of esophagus, stomach. Potential symptoms of overexposure by fume inhalation are severe respiratory tract irritation, pulmonary edema. Direct contact may cause vesicular eruptions on skin and eczematoid dermatitis. *See Clinical Toxicology of Commercial Products*, R. E. Gosselin *et al.*, Eds. (Williams & Wilkins, Baltimore, 5th ed., 1984) Section III, pp 202-205.

USE: Aq soln as bleach, disinfectant; chlorination of swimming pools; sanitation of drinking water.

THERAP CAT: Antiseptic, disinfectant.

8703. Sodium Hypophosphite. [7681-53-0] Phosphinic acid, sodium salt. H_2NaO_2P; mol wt 87.98. H 2.29%, Na 26.13%, O 36.37%, P 35.21%. NaH_2PO_2. Solubility data: Palit, *J. Am. Chem. Soc.* **69,** 3120 (1947).

Monohydrate. White, odorless, deliquesc granules; saline taste. When strongly heated, it dec with evolution of phosphine which ignites spontaneously in the air. *It explodes when triturated with chlorates or other oxidizing agents.* Sol in 1 part water, 0.15 part boiling water; freely sol in glycerol and in boiling alcohol; sol in cold alcohol, slightly in abs alcohol. Insol in ether. Soly of anhydr NaH_2PO_2 at 25° in ethylene glycol: 33.0 g/100 g; in propylene glycol: 9.7 g/100 g. The aq soln is neutral. *Keep well closed.*

USE: As reagent for arsenic and iodates; prepn of hypophosphites syrup.

8704. Sodium Iodate. [7681-55-2] $INaO_3$; mol wt 197.89. I 64.13%, Na 11.62%, O 24.25%. $NaIO_3$. The article of commerce contains about 99% $NaIO_3$. Acute toxicity study: S. H. Webster *et al., J. Pharmacol. Exp. Ther.* **120,** 171 (1957). Review of safety assessment: *J. Am. Coll. Toxicol.* **14,** 231-239 (1995).

White, cryst powder. d 4.28. Sol in acetone, acetic acid. Sol in ~11 parts water, 3 parts boiling water. Insol in alc. The aq soln is neutral. LD_{50} in female mice (mg/kg): 119 ±4 i.p., 108 ±4 i.v., 505 ±26 orally (Webster).

THERAP CAT: Antiseptic (mucous membranes).

8705. Sodium Iodide. [7681-82-5] Ioduril; Anayodin. INa; mol wt 149.89. I 84.67%, Na 15.34%. NaI. U.S.P. NaI is at least 99% pure.

White, odorless, deliquesc crystals or granules. Gradually absorbs up to about 5% (½ mol) moisture on exposure to air. Slowly becomes brown in the air due to liberation of iodine. Its aq soln is similarly affected. d 3.67. mp 651°. One gram dissolves in 0.5 ml water, ~2 ml alc, 1 ml glycerol; sol in acetone. It is made slightly alkaline to render it more stable. pH: 8-9.5. *Keep well closed and protected from light.* At ordinary room temp crystallizes from water with $2H_2O$ in the form of colorless, prismatic crystals. *Incompat.* As of potassium iodide. MLD i.v. in rats: 1.3 g/kg, Loeser, Konwiser, *J. Lab. Clin. Med.* **35** (1929).

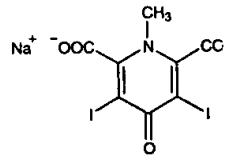
THERAP CAT: Iodine supplement; expectorant.

THERAP CAT (VET): Actinobacillosis, actinomycosis. Expectorant. Has been used for ringworm, hyperplastic fibrous sions, paraplegia from pachymeningitis of dogs.

8706. Sodium Iodide, Radioactive. radio-iodide (^{131}I); sodium iodide—^{131}I; iodide; Radiocaps-131; Theriodide-131. I iodine (^{131}I) which has a half-life of 8 da gamma rays. Other properties identical sodium iodide. Dispensed as carrier-free capsules for oral use or in aq soln for or istration.

THERAP CAT: Diagnostic aid (thyroid tic.

8707. Sodium Iodomethamate. [5 3,5-diiodo-1-methyl-4-oxo-2,6-pyridined dium salt; 3,5-diiodo-1-methylchelidami sodium *N*-methyl-3,5-diiodo-4-pyridone doxyl; D-40; Neo-Iopax; Pyelectan; Ur mol wt 492.90. C 19.49%, H 0.61%, I 9.33%, O 16.23%. Prepn: Chelidonic ac damic acid by the action of NH_3, chelic with iodine in a boiling aq alkaline soln methylated at the nitrogen with dimet fine soln, *cf.* Dohrn, Diedrich, *Ann.* 545916; DE 545266; DE 556142; US 1



Crystals, dec around 200° with effer water (1:1). Practically insol in chlorof ether.

THERAP CAT: Diagnostic aid (radiopa

8708. Sodium Isopropyl Xantha pyxanthic acid sodium salt; Good-Rite wt 158.22. C 30.37%, H 4.46%, Na 40.53%. $(CH_3)_2CHOCSSNa$.

Deliquescent, white to yellowish pow slightly unpleasant odor. Soly in water: 54% at 35°.

Caution: Irritating to skin, eyes, m ratory tract.

USE: Control of annual weeds in be

8709. Sodium Lactate. [72-17-3 mol wt 112.06. C 32.15%, H 4.50%, Commercially available as a mixture w 60% sodium lactate. *Ref:* Shaw, US Dairy Prod. Corp.).

Colorless or almost colorless, thick, c with water, alcohol. The soln is neutral

USE: Instead of glycerol in calico casein; as a corrosion inhibitor in a

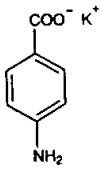
THERAP CAT: Electrolyte replenishe alizer.

THERAP CAT (VET): Has been used i

8710. Sodium Lauryl Sulfate. | monododecyl ester sodium salt; sodiu lauryl sulfate. $C_{12}H_{25}NaO_4S$; mol wt 288.38. 4.97%, O 22.19%, S 11.12%. $CH_3(C$ anionic detergent prepd by sulfation of la and neutralization with sodium carbonate: Colloid-Z. 63, 50 (1933). Surfactant Addison, *Trans. Faraday Soc.* **33,** Ind. Eng. Chem. **36,** 610 (1944 and mol wt estimation of protei Biochem. Biophys. Res. Commun. **28** Osborn, *J. Biol. Chem.* **244,** 4406 B. S. Leach *et al., Biochemistr* study: A. I. T. Walker *et al., Foo*

ım Acetate. [127-08-2] $C_2H_3KO_2$; mol
l 3.08%, K 39.84%, O 32.61%. CH_3CO
ıs, rapidly deliquesc crystals or white
d^{25} 1.57. mp 292°. One gram dissol
ıl boiling water, 2.9 ml alcohol. The a
:. pH of 0.1 molar aq soln 9.7. *Keep*
in rats: 3.25 g/kg, H. F. Smyth *et al*
30, 470 (1969).
ikalizer.
): Has been used in cardiac arrhythm
uretic.

ım *p*-Aminobenzoate. [138-84-1]
d potassium salt; potassium *para*-amino
taba. $C_7H_6KNO_2$; mol wt 175.23. C 47.9
%, N 7.99%, O 18.26%. Prepn: E. A. M
. Soc. 89, 3565 (1967). Crystal structur
ıpt. Rend. Ser. C 267, 1402 (1968).
diopathic pulmonary fibrosis: U. H. C
ie 152, 75 (1975); in Peyronie's disease
Sex. Med. 6, 29 (1970); G. Williams,
ol. 52, 392 (1980).



alcohol. Saline taste. Slightly alkaline
soln about 7. Very freely sol in water, le
y insol in ether. Reported to cause less g
: free acid or the sodium salt.
in the manuf of condensation polymer
.
Antifibrotic.

ssium Arsenate. [7784-41-0] Potassium
ium dihydrogen arsenate; Macquer's
vt 180.03. As 41.62%, H 1.12%, K 21.72
O_4.
tals or white, cryst mass or powder. *Poiso*
. parts cold, more sol in hot water, slowly
nsol in alcohol.
extile, tanning, and paper industries. In
ons (especially fly paper).

ıssium Arsenite. [13464-35-2] Comm
as variable composition; approx KH(As
data: A. J. Lehman, *Quart. Bull. Assoc*
15, 122 (1951). Evaluation of carcinogen
phs 2, 48-73 (1973); *Comm. Eur. Comm*
3, 53-58 (1991).
scopic powder; gradually dec on exposure
Very poisonous! Sol in water. *Keep well*
ats: 14 mg/kg (Lehman).

rsenite solution. [1332-10-1] Fowler's
olution. Prepd by dissolving arsenic tri
icarbonate and ethanol. Toxicity study: H
iron. Health Perspec. 95, 205 (1991).
ıuf of mirrors to reduce the silver salt to m

Fowler's soln formerly as antineoplastic

VET): Fowler's soln has been used as an
in pulmonary emphysema, chronic cough
kin diseases.

tassium Bicarbonate. [298-14-6] Pot
; K-Lyte. $CHKO_3$; mol wt 100.12. C 12.0
5%, O 47.94%. $KHCO_3$. Contains not le

is section.

ess, transparent crystals, white granules or powder. Sol
8 parts water, 2 parts water at 50°. Almost insol in alcohol.
8.2 (in 0.1 molar concn).
In baking powders, effervescent salts.
ERAP CAT: Potassium supplement.

7692. Potassium Bifluoride. [7789-29-9] Potassium acid
ride; potassium hydrogen fluoride. F_2HK; mol wt 78.10. F
65%, H 1.29%, K 50.06%. KF.HF. Prepd according to the
KOH + 2HF = KHF_2 + H_2O: Lange, Eichler, *Z. Physik.*
, 129, 285 (1927); Kwasnik in *Handbook of Preparative*
rganic Chemistry vol. 1, G. Brauer, Ed. (Academic Press,
York, 2nd ed., 1963) p 237. Made commercially from
ssium carbonate and hydrofluoric acid.
Tetragonal crystals. *Poisonous!* d 2.37. mp 238.7°. Trans-
rmation pt 195°. Soly in water (g/100 ml): 30.1 (10°); 39.2
0°); 114.0 (80°). Sol in dil alc. Insol in abs alc.
Caution: Corrosive and irritating to skin, mucous mem-
anes.
: In the prepn of pure potassium fluoride; as an electro-
te in the manuf of fluorine; frosting glass; treating coal to
vent slag formation; flux for silver solders; catalyst in the
kylation of benzene with olefins.

7693. Potassium Binoxalate. [127-95-7] Potassium acid
alate; salt of sorrel; sal acetosella. C_2HKO_4; mol wt 128.13.
18.75%, H 0.79%, K 30.51%, O 49.95%. KOOCCOOH. In-
rrectly *"salt of lemon"*. The same synonyms apply to potas-
m tetraoxalate.
Monohydrate. White, odorless crystals. *Poisonous!* d 2.0.
l in 40 parts cold, 6 parts boiling water, slightly in alcohol.
H of 0.1 molar aq soln: 2.7.
: Removing ink stains, scouring metals, cleaning wood;
otography; as mordant in dyeing; bleaching stearic acids.

7694. Potassium Biphthalate. [877-24-7] Phthalic acid
tassium acid salt; potassium acid phthalate; potassium hy-
gen phthalate; acid potassium phthalate. $C_8H_5KO_4$; mol wt
04.22. C 47.05%, H 2.47%, K 19.15%, O 31.34%. $HOOCC_6$-
$COOK$. Prepd by half-neutralization of a phthalic anhydride
te: F. J. Welcher, *Organic Analytical Reagents* vol. 2 (Van
strand, New York, 1947) pp 75-79.
Orthorhombic crystals, stable in air. d_4^{25} 1.636. Acid reaction;
H of 0.05*M* aq soln at 25° = 4.005 (glass electrode). Sol in
out 12 parts cold water, 3 parts boiling water; slightly sol in
cohol.
: As primary standard for preparing volumetric alkali
ns; also as a buffer in pH determinations.

7695. Potassium Bisulfate. [7646-93-7] Potassium acid
fate; potassium hydrogen sulfate; sal enixum. HKO_4S; mol
136.17. H 0.74%, K 28.71%, O 47.00%, S 23.55%. $KHSO_4$.
White, deliquesc crystals, pieces, or granules. d 2.24. mp
0°, at higher temp loses water and is converted into pyrosul-
te. Sol in 1.8 parts water, 0.85 part boiling water. *Keep well*
sed.
: As flux in analysis of ores and siliceous compds.
ERAP CAT: Cathartic.

7696. Potassium Bisulfide. [1310-61-8] Potassium hy-
sulfide; potassium hydrogen sulfide; potassium sulfhydrate.
HS; mol wt 72.17. H 1.40%, K 54.17%, S 44.43%. KHS.
Prepd industrially from $Ca(HS)_2$ and K_2SO_4: Hene, DE 380385
(1922); from H_2S and K_2S: Bassett, US 1662735 (1925); Stro-
acker, Jones, US 1771384 (1926 to Dow). Prepn of pure ma-
rial by the action of dry H_2S upon potassium metal dissolved
absolute ethanol: Rule, *J. Chem. Soc.* 99, 558, 564 (1911); West,
Z. Kryst. 88, 102 (1934).
Colorless, deliquescent crystals or white, strongly hygro-
opic, cryst mass. Usually present as the hemihydrate. Tri-
inal system. d 1.70. Rapidly becomes yellow on exposure to
r with formation of polysulfides and H_2S. Becomes anhydr at
75-200°. mp 450-510° forming a dark red liquid. Heat of for-
ation: +62.5 kcal. Heat of soln at 17°: +0.77 kcal, for hem-
ydrate at 16°: +0.62 kcal. Freely sol in water, alcohol.

7697. Potassium Bitartrate. [868-14-4] Potassium acid
rtrate; acid potassium tartrate; potassium hydrogen tartrate;
cream of tartar; cremor tartari; faecula; faecla. $C_4H_5KO_6$; mol wt 188.18. C 25.53%, H 2.68%, K 20.78%, O 51.01%. $KHC_4H_4O_6$. Obtained from the sediments in the manuf of wine, known as argols or wine lees. The salt is at least 99.5% pure. *See also* Argol and Tartaric Acid.

Colorless crystals or white, cryst powder; pleasant acidulous taste. One gram dissolves in 162 ml water, in 16 ml boiling water, 8820 ml alcohol; readily sol in dil mineral acids, in solns of alkalies or borax. Soly in water also given as about 0.4% at 10° to about 6% at 100°.

USE: Largely in baking powders; coloring metals, galvanic tinning of metals; reducer of CrO_3 in mordants for wool.

THERAP CAT: Cathartic.

THERAP CAT (VET): Laxative, diuretic.

7698. Potassium Borohydride. [13762-51-1] Potassium tetrahydroborate. BH_4K; mol wt 53.94. B 20.04%, H 7.47%, K 72.48%. KBH_4. Prepn: H. I. Schlesinger *et al., J. Am. Chem. Soc.* 75, 199 (1953). Commercial process: M. D. Banus *et al., ibid.* 76, 3848 (1954). NMR relaxation study: T. Tsang, T. C. Farrar, *J. Chem. Phys.* 50, 3498 (1969); IR and Raman spectra: K. B. Harvey, N. R. McQuaker, *Can. J. Chem.* 49, 3272 (1971). Use as reducing agent in protein labelling: E. K. J. Pauwels *et al., Nucl. Med. Biol.* 20, 825 (1993); in simple reductions: C. Than *et al., J. Label. Compd. Radiopharm.* 38, 693 (1996); J. C. Briggs *et al., Tetrahedron* 53, 3943 (1997). Review of potassium and other metal tetrahydroborates: B. D. James, M. G. H. Wallbridge, *Prog. Inorg. Chem.* 11, 99-231 (1970).

Non-hygroscopic crystals. Stable to air. d 1.11. n_D +1.490. Dec commences at about 500°. Supports combustion. Negative heat of soln in H_2O = 6.3 kcal/mol. Soly (w/w) in water at 25°: 19%; liq ammonia at 25°: 20%; ethylenediamine at 75°: 3.9%; methanol at 20°: 0.7%; DMF at 20°: 15.0%. 0.25 g dissolves in 100 g of 95% ethanol at 25°. Soly in a 4:1 water-methanol mixture: 13 g/100 g. Insol (< 0.01%) in isopropylamine, benzene, hexane, ether, dioxane, tetrahydrofuran and acetonitrile. Alkaline aq solutions are stable.

USE: Reducing agent; source of H^-.

7699. Potassium Borotartrate. [12001-68-2] Potassium tartratoborate; soluble cream of tartar; borated cream of tartar; potassium sodium borotartrate. Made by evaporating a soln of 2 parts borax and 7 parts potassium bitartrate.

White, odorless powder. Freely sol in water.

USE: Has been used in photography as a retarder for alkaline developers.

7700. Potassium Bromate. [7758-01-2] $BrKO_3$; mol wt 167.00. Br 47.85%, K 23.41%, O 28.74%. $KBrO_3$.

White crystals or granules. d 3.27. mp about 350°, decomposing at about 370° with evolution of oxygen. Sol in 12.5 parts water, 2 parts boiling water. Almost insol in alc.

Caution: Ingestion may cause vomiting, diarrhea, methemoglobinemia, renal injury.

USE: Bread- and flour-improving agent; in analytical chemistry.

7701. Potassium Bromide. [7758-02-3] BrK; mol wt 119.00. Br 67.15%, K 32.86%. KBr. Continuous electrolytic process of prepn: Maylott, Elkins, US 2989450 (1961 to Dow).

Colorless crystals or white granules or powder. d 2.75. mp 730°. One gram dissolves in 1.5 ml water, 1 ml boiling water, 250 ml alc, 4.6 ml glycerol. The aq soln is neutral.

Caution: Large doses cause CNS depression. Prolonged intake may cause mental deterioration, acneform skin eruptions.

USE: Manuf photographic papers and plates; process engraving.

THERAP CAT: Sedative, anticonvulsant.

THERAP CAT (VET): Sedative.

7702. Potassium Carbonate. [584-08-7] Salt of tartar; pearl ash. CK_2O_3; mol wt 138.21. C 8.69%, K 56.58%, O 34.73%. K_2CO_3.

Hygroscopic, odorless granules or granular powder. d 2.29; mp 891°. Sol in 1 part cold, 0.7 part boiling water. Practically insol in alcohol. Its aq soln is strongly alkaline. pH 11.6. *Keep tightly closed.* LD_{50} orally in rats: 1.87 g/kg. H. F. Smyth *et al., Am. Ind. Hyg. Assoc. J.* 30, 470 (1969).

Sesquihydrate. Small granular crystals. When it contains the full amount of water (16.36%) it is not hygroscopic. Sol in less than 1 part water. Practically insol in alcohol. The aq soln is strongly alkaline.

Caution: Irritant, caustic.

USE: Manuf soap, glass, pottery, smalts and many potassium salts; in process engraving and lithography; tanning and finishing leather; liq shampoos; for removal of water from organic liqs; in anal. chemistry.

THERAP CAT: Alkalizer, diuretic.

7703. Potassium Chlorate. [3811-04-9] Potcrate. $ClKO_3$; mol wt 122.55. Cl 28.93%, K 31.90%, O 39.17%. $KClO_3$. Contains at least 99% $KClO_3$.

Colorless, lustrous crystals, or white granules or powder. d 2.32. mp 368°; above this temp it dec into perchlorate and oxygen. One gram dissolves slowly in 16.5 ml water, 1.8 ml boiling water, about 50 ml glycerol. Almost insol in alcohol. *Keep out of contact with organic matter or other oxidizable substances. Caution:* Explodes with sulfuric acid; inflames with explosion if triturated with any organic substances, sulfur, phosphorus, sulfite, hypophosphite, and other oxidizable substances. *Incompat.* Iodides, tartaric acid.

Caution: Irritating to G.I. tract, kidney; can cause hemolysis of red blood cells and methemoglobinemia: *Clinical Toxicology of Commercial Products,* R. E. Gosselin *et al.,* Eds. (Williams & Wilkins, Baltimore, 5th ed., 1984) Section II, p 112; Section III, pp 74-77.

USE: Explosives; fireworks; matches; printing and dyeing cotton and wool black; manuf aniline black and other dyes; source of oxygen; in chemical analyses.

THERAP CAT: Formerly as topical antiseptic.

THERAP CAT (VET): In dilute soln as antiseptic mouthwash.

7704. Potassium Chloride. [7447-40-7] Chloropotassuril; Diffu-K; Enseal; Kaleorid; Kalitabs; Kalium-Duriles; Kaon-Cl; Kaskay; Kayback; Kay-Cee-L; K-Contin; Klor-Con; K-Norm; K-Tab; Lento-Kalium; Micro-K; Nu-K; Peter-Kal; PfiKlor; Rekawan; Repone K; Slow-K; Span-K. ClK; mol wt 74.55. Cl 47.56%, K 52.45%. KCl. Occurs in nature as the mineral *sylvine* or *sylvite*. Industrial prepns: *Faith, Keyes & Clark's Industrial Chemicals,* F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 666-673.

White crystals or crystalline powder. d 1.98. mp 773°. One gram dissolves in 2.8 ml water, 1.8 ml boiling water, 14 ml glycerol, about 250 ml alcohol. Insol in ether, acetone. Hydrochloric acid, sodium or magnesium chlorides diminish its soly in water. d of saturated aq soln at 15° is 1.172. pH: about 7.

Caution: Large doses by mouth can cause G.I. irritation, purging, weakness and circulatory disturbances.

USE: In photography. In buffer solns, electrode cells.

THERAP CAT: Electrolyte replenisher.

THERAP CAT (VET): Potassium supplement.

7705. Potassium Chromate(VI). [7789-00-6] Neutral potassium chromate. CrK_2O_4; mol wt 194.19. Cr 26.78%, K 40.27%, O 32.96%. K_2CrO_4.

Lemon-yellow crystals; d 2.73; mp 975°. Sol in 1.6 parts cold, 1.2 parts boiling water. Insol in alcohol. The aq soln is alkaline to litmus or phenolphthalein.

USE: Has a limited application in enamels, finishing leather, rustproofing of metals, being replaced by the sodium salt; as reagent in analytical chemistry.

7706. Potassium Citrate. [866-84-2] Urocit-K. $C_6H_5K_3O_7$; mol wt 306.39. C 23.52%, H 1.64%, K 38.28%, O 36.55%. $K_3C_6H_5O_7$. It is at least 99% pure.

Monohydrate. White crystals, granules or powder. Loses its water at 180°. One gram dissolves in 0.65 ml water; very slowly in 2.5 ml glycerol. Practically insol in alcohol. The aq soln is alkaline to litmus; pH about 8.5.

THERAP CAT: Antiurolithic. Antacid.

THERAP CAT (VET): Diuretic.

7707. Potassium Citrate, Monobasic. [866-83-1] Monopotassium citrate. $C_6H_7KO_7$; mol wt 230.21. C 31.30%, H 3.06%, K 16.98%, O 48.65%. $KH_2C_6H_5O_7$.

White, cryst powder. Sol in water; the soln is subject to molding.

USE: A 0.05 molal solution as standard for pH scale (pH at 25° 3.776): Staples, Bates, *J. Res. Nat. Bur. Stand.* **73A,** 37 (1969).

7708. Potassium Cyanate. [590-28-3] CKNO; mol wt 81.12. C 14.81%, K 48.20%, N 17.27%, O 19.72%. Inhibitor of sickling of erythrocytes *in vitro:* Cerami, Manning, *Proc. Nat. Acad. Sci. USA* **68,** 1180 (1971). *See also* Sodium Cyanate. Pharmacology: A. Cerami *et al., J. Pharmacol. Exp. Ther.* **185,** 653 (1973). Brief review: *Dangerous Prop. Ind. Mater. Rep.* **13,** 408-415 (1993).

White, cryst powder. d 2.05. Sol in water, very slightly in alcohol. LD_{50} i.p. in mice: 320 mg/kg (Cerami).

7709. Potassium Cyanide. [151-50-8] CKN; mol wt 65.12. C 18.44%, K 60.04%, N 21.51%. KCN. The article of commerce contains about 95% KCN. Toxicity study: Hayes, *Toxicol. Appl. Pharmacol.* **11,** 327 (1967).

White, deliquesc, granular powder or fused pieces; odor of HCN. *Violent poison!* On exposure to air it is gradually dec by CO_2 and moisture. d 1.52; mp 634°. Sol in 2 parts cold, 1 part boiling water, 2 parts glycerol, 100 parts alcohol, 25 parts methanol. The aq soln is strongly alkaline and rapidly dec. pH of 0.1*N* aq soln: 11.0. *Keep tightly closed and protected from light. Incompat.* Acids and acid syrups; alkaloids, chloral hydrate, iodine, metallic salts, permanganates, chlorates, peroxides. LD_{50} orally in rats: 10 mg/kg (Hayes).

Caution: Potential symptoms of overexposure are irritation of eyes, skin and upper respiratory system; weakness, headache and confusion; nausea, vomiting; increased rate of respiration; slow gasping respiration; asphyxia; thyroid and blood changes. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 262.

USE: Similar to sodium cyanide.

7710. Potassium Dichromate(VI). [7778-50-9] Potassium bichromate. $Cr_2K_2O_7$; mol wt 294.18. Cr 35.35%, K 26.58%, O 38.07%. $K_2Cr_2O_7$. In the U.S.A. it is usually prepared by the reaction of potassium chloride on sodium dichromate: Vetter in *Kirk-Othmer Encyclopedia of Chemical Technology* **vol. 3** (Interscience, New York, 1949) p 951; Hartford, Copson, *ibid.* **vol. 5** (2nd ed., 1964) pp 484-488. In Germany it is obtained from potassium chromate produced by roasting the chrome ore with KOH. *Ref:* Müller, Glissmann in *Ullmann's Encyklopädie der Technischen Chemie,* **vol. 5** (Munich, 3rd ed., 1954) p 580.

Bright orange-red crystals. Not hygroscopic or deliquescent (difference from sodium dichromate). Crystal habit: prismatic. Crystal system: triclinic pinacoidal, transition to monoclinic at 241.6°. d_4^{25} 2.676. Bulk density: 100 lbs/cu ft. mp 398°. Dec at about 500°. Heat of fusion 29.8 cal/g. Heat of soln −62.5 cal/g. Specific heat 0.186 at 16° −98°. Soluble in water. A sat'd aq soln contains at 0°: 4.3%, at 20°: 11.7%, at 40°: 20.9%, at 60°: 31.3%, at 80°: 42.0%, at 100°: 50.2%. Acid reaction: A 1% aq soln has a pH of 4.04 and a 10% soln has a pH of 3.57.

Caution: Intern. a corrosive poison. Industrial contact may result in ulceration of hands, destruction of mucous membranes and perforation of nasal septum. *See* E. Browning, *Toxicity of Industrial Metals* (Appleton-Century Crofts, New York, 2nd ed., 1969) pp 119-131. *See also* Chromium.

USE: In tanning leather, dyeing, painting, decorating porcelain, printing, photolithography, pigment-prints, staining wood, pyrotechnics, safety matches; for bleaching palm oil, wax, and sponges; waterproofing fabrics; as oxidizer in the manuf of organic chemicals; in electric batteries; as depolarizer for dry cells. As corrosion inhibitor in preference to sodium dichromate where lower soly is advantageous. Pharmaceutic aid (oxidizing agent).

THERAP CAT (VET): Caustic.

7711. Potassium Dicyanoaurate(I). [13967-50-5] Gold potassium cyanide; potassium aurocyanide. C_2AuKN_2; mol wt 288.10. C 8.34%, Au 68.37%, K 13.57%, N 9.72%. $KAu(CN)_2$. Prepd by electrolysis of Au in KCN: Glassford, Napier, *Phil. Mag.* **25,** 61 (1844).

Dihydrate. Cryst powder. One gram ... 0.5 ml boiling water; slightly sol in alc... in ether.

USE: For electroplating.

7712. Potassium Ferricyanide. [1... ...sium hexakis(cyano-*C*)ferrate(3−); pot... ...rate(III); red prussiate of potash. C_6FeK_3... 21.89%, Fe 16.96%, K 35.62%, N 25.53...

Ruby-red crystals. d 1.89. Slowly sol i... in 1.3 parts boiling water; slightly sol in ... aq soln dec slowly on standing. *Protect ...*

USE: Chiefly for blueprints; in photogr... wood, dyeing wool, calico printing, as etc... liquor), tempering iron and steel; in elec... oxidizing agent in organic synthesis; in a...

7713. Potassium Ferrocyanide. ...potassium hexakis(cyano-*C*)ferrate(4− ...cyanoferrate(II); yellow prussiate of potas... 368.35. C 19.56%, Fe 15.16%, K 42.4... $Fe(CN)_6$. Review of properties, chemistr... *Chemistry of Ferrocyanides,* American C... Press, New York, 1953) 112 p.

Trihydrate. Soft, slightly efflorescen... lose water at 60°, becomes anhydr at 100°

7714. Potassium Fluoride. [7789-... 28.10. F 32.70%, K 67.29%. KF. Prepd ... KHF_2 or by neutralizing HF with K_2CO... *Physik. Chem.* **129,** 285, 286 (1927); Kwa... *Preparative Inorganic Chemistry* **vol. 1,** ... demic Press, New York, 2nd ed., 1963) p ... Simonin, *Compt. Rend. Soc. Biol.* **124,** 13... Cubic crystals (NaCl lattice). Usually ol... liquesc powder or solid. *Poisonous!* d 2.... 1505°. Soly in water (g/100 ml): 92.3 (18... freely sol in boiling water. Also sol in aq ... alcohol unless water is present. May be ... containers. Attracts moisture from the ai... glass and porcelain. MLD in guinea pigs ... 250 s.c.; in frogs (mg/kg): 375 s.c. (Simon...

Dihydrate. Monoclinic crystals, mp ... (18°): 349.3 g/100 ml.

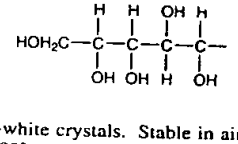
Tetrahydrate. Crystals, mp 19.3°.

Caution: Irritating to skin, eyes, mucou...

USE: In the fluorination of organic com... solder; to prevent unwanted fermentations ... solutions; for frosting glass.

7715. Potassium Formate. [590-29-... 84.12. C 14.28%, H 1.20%, K 46.48%, O ... Colorless, deliquesc granules. d 1.91. mp ... decomp with evolution of H_2. Sol in 0.4 part ... Practically neutral. *Keep tightly closed.*

7716. Potassium Gluconate. [2... ...tassium salt; Gluconsan K; Kal... ...bral; Potassuril; K-IAO; ... 234.25. C 30.76%, H 4.73%, K ... ...tassium salt of gluconic acid.



Yellowish-white crystals. Stable in air. M... dec 180°. Freely sol in water. Prac... alcohol, ether, benzene, chloroform. Aq so... gives and have a pH of 7.5-8.5.

THERAP CAT: Replenisher (electrolyte).

THERAP CAT (VET): Potassium supplement

7717. Potassium Glycerophosphate. ... $C_3H_7KO_6P$; mol wt 248.25. C 14.51%, H 2.8... 15.67%, P 12.48%. $K_2C_3H_7PO_6$.

Cons...

Enhancement of *Candida antarctica* lipase B enantioselectivity and activity in rganic solvents

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The enantioselectivity and catalytic activity of Novozym 435® [*Candida antarctica* lipase B (CALB)] in organic solvents was found to dramatically increase upon the addition of a non-reactive organic base, such as Et_3N, to the reaction system.

It has been shown that the unusual microenvironment of enzymes in organic solvents can affect a number of parameters, including the degree of protein hydration,[1,2] secondary structure,[3] the susceptibility of the protein to inactivation and variations in the ionisation state[4] of side-chain residues. Frequently, these differences have been shown to result in interesting changes in the enzymes, including reversal of substrate specificity and changes in stereoselectivity, although the underlying reasons remain poorly understood.

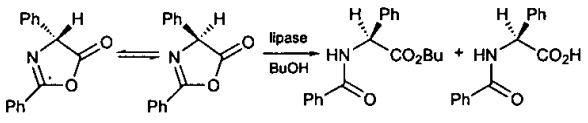
It is commonly accepted that the best predictor of enzyme catalytic activity in low water organic media is thermodynamic water activity (a_w).[1]‡ Over the past few years although much has been reported on enzyme enantioselectivity in organic media there are as yet no predictive rules available. Crude lipase preparations have proved to be simple and effective biocatalysts for kinetic resolutions, *e.g.* chiral carboxylic acids and alcohols. However, the low purity of these preparations (presence of other lipases and competing hydrolases) can, in specific reactions, lead to low and unpredictable enantioselective behaviour. This effect can be compounded when using organic solvents, due to the effect of different solvent properties on catalytic activity.

The starting point for the work described herein was the lipase (Lipozyme® *Mucor miehei*) catalysed dynamic resolution of 4-substituted oxazol-5(4*H*)-ones, a reaction we have previously employed for the synthesis of enantiomerically pure (*S*)-L-*tert*-leucine.[5] It was previously found that the modest enantioselectivity in toluene (*ca.* 68% ee) could be enhanced (*ca.* 97% ee) by the addition of a catalytic amount of Et_3N to the reaction; the role of Et_3N is not to facilitate racemisation of the substrate.

We decided to investigate this effect in more detail by using a commercially available immobilised lipase,§ Novozym 435 (*Candida antarctica* lipase B[6] (CALB), since a larger substrate range could be tested with this enzyme. The catalytic activity and enantioselectivity of the alcoholysis of (±)-2-phenyl-4-benzyloxazol-5(4*H*)-one **1** using butan-1-ol as the nucleophile (Scheme 1) was monitored¶ under a range of reaction conditions, including controlled water activity. Hydration was controlled by equilibrating‖ enzyme and solvent with the appropriate saturated salt solution[7] of known thermodynamic water activity a_w. Therefore a low a_w system will be one in which the solvent is poorly hydrated and the enzyme, similarly, has a low level of hydration, and at high a_w (*e.g.* 0.97) the solvent is near water saturation and the enzyme is fully hydrated (as would be found in an aqueous system). Table 1 shows the effect of hydration on the initial catalytic rate and enantioselectivity, in three different solvents, n-hexane, toluene and MeCN, either with or without Et_3N.**

It can immediately be seen that the lipase-catalysed reaction is very sensitive to water activity. The addition of a non-reactive organic base,†† Et_3N, to the reaction enhances significantly both the enantioselectivity and catalytic activity of the enzyme. Even low levels of hydration, present in the more nonpolar solvents such as n-hexane and toluene, are detrimental to the overall catalytic performance of CALB. We find that generally for optimum yield and enantioselectivity, both the enzyme and solvent should be rigorously dried prior to addition of Et_3N. We were interested to see if addition of Et_3N to a reaction already in progress and of poor enantioselectivity, could reverse this effect. As can be seen from Fig. 1, the addition of Et_3N after 140 min immediately results in enhanced catalytic rate and enantioselectivity.

In order to examine the generality of the effect of Et_3N we investigated a second reaction, namely the CALB-catalysed



Scheme 1

Table1 Effect of water activity on initial catalytic rate[a,b] and enantiospecificity as a function of hydration, with and without Et_3N

		No Et_3N		Et_3N	
Solvent[c]	a_w	Initial rate/nmol min^{-1} mg^{-1}	Ee (%)	Initial rate/nmol min^{-1} mg^{-1}	Ee (%)
n-hexane	~0 (anhydrous)	26 (± 1.5)	85 (± 3)	30 (± 1.5)	90 (± 3)
n-hexane	0.69	4 (± 0.5)	55 (± 2)	20 (± 1)	87 (± 3)
n-hexane	0.97	1.5 (± 0.15)	30 (± 5)	18 (± 0.9)	80 (± 5)
toluene	~0	15 (± 0.8)	85 (± 4)	27 (± 1.5)	93 (± 3)
toluene	0.22	3	61 (± 6)	17 (± 1)	95 (± 2)
MeCN[d]	~0	15	>99	10	97 (± 2)
MeCN[d]	0.1 (0.5% v/v H_2O)	NR[e]	—	5 (± 0.3)	90 (± 4)
MeCN[d]	0.4 (2% v/v H_2O)	NR[e]	—	NR[e]	—

[a] Initial rate for (*S*)-butyl ester enantiomer **2**. [b] Results reported are the average of three separate measurements. [c] Note ‖. [d] Ref. 8. [e] No reaction.

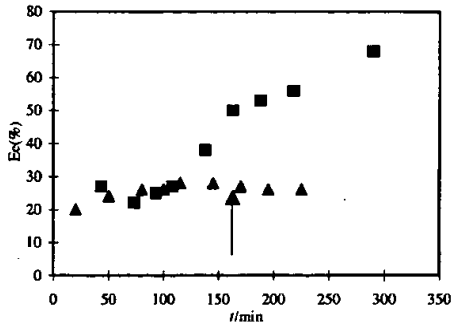


Fig. 1 Effect of Et_3N on ee. Reactions A (▲) and B (■) were carried out under identical conditions (a_w = 0.69). At t = 140 min, 14 mol% Et_3N was added to reaction B (arrow).

reaction between 1-phenylacetoxy-2-methylcyclohexene and butanol yielding 2-methylcyclohexanone and butyl phenylacetate.[9,15] Using n-hexane (a_w = 0) and MeCN (0.5% H_2O, a_w = 0.1) as the solvents, we observed that the addition of Et_3N to the solvent resulted in a dramatic increase in the catalytic activity. An approximate 200-fold increase in activity was observed in MeCN (a_w = 0.1) and a 700-fold one for that in n-hexane (a_w = 0.97). The higher activity found in n-hexane is presumably due to a more intimate contact between the enzyme and Et_3N in a more nonpolar environment. Similarly, the activation effect for (±)-2-phenyl-4-benzyloxazol-5(4*H*)-one ring-opening in MeCN is similar to that described above and is expected to be a result of less Et_3N adsorption to the enzyme in MeCN.

The ability of organic bases to increase the enantioselectivity of lipase-catalysed reactions in water-saturated organic solvents has previously been reported.[10–13] In some cases[11,12] this effect has been attributed to the formation of an ion-pair between the base and any by-product acid. Using electrospray ionisation mass spectrometry (ESI-MS)‡‡ we have detected the formation of carboxylic acid **3** during the course of the oxazolone reaction at intermediate to high water activities (*e.g.* a_w = 0.69–0.97). We have also found that addition of acid **3** to an already hydrated system results in loss of activity, which can be fully recovered upon addition of an organic base, presumably *via* formation of an ion pair. Ion pair formation is observed in both low and high dielectric non-hydrogen bonding solvents such as n-hexane and MeCN. In a high dielectric, non-hydrogen bonding solvent such as MeCN, where the acid was found to be more soluble, we find experimentally that dissolution of acid **3** in n-hexane and MeCN occurs upon addition of Et_3N, thus removing acid from the immediate microenvironment of the enzyme. However, the enhancement of catalytic performance and enantioselectivity for rigorously dried samples, and those of low water activity (a_w < 0.7) where we find no evidence for hydrolysis over the course of the initial rate measurement, cannot be explained in terms of hydrolysis products affecting enantioselectivity, since for an unrelated substrate, an activating effect on the catalytic activity has been demonstrated.

The addition of co-solvents, such as DMF and DMSO, was found to solubilise the acid and thus it was anticipated that they would perform a similar role to Et_3N in removing any acid from the immediate vicinity of the enzyme. Both DMF and DMSO were chosen as additives to the bulk organic solvent (toluene at a_w = 0.22). Although both DMF and DMSO increased the enantioselectivity of the reaction to 85% ee, there was no significant effect on the catalytic rate as found with Et_3N. Since the solvation of the carboxylic acid by these co-solvents occurs by a different mechanism to that of Et_3N, *i.e.* the additives are unable to form ion-pairs, they have limited use in reducing the overall effect.

The role of Et_3N therefore appears to be dual in nature, *i.e.* increasing both the enantioselectivity and catalytic activity of lipase-catalysed reactions. The addition of Et_3N therefore provides an additional strategy for improving the enantioselectivity of lipase-catalysed reactions. We are currently investigating this effect with other lipolytic enzymes.

We are grateful to Boehringer Mannheim, Germany, for the generous gift of lipase samples. The BBSRC is acknowledged for a David Phillips Fellowship (M. C. P.) and a studentship (S. A. B.).

Notes and References

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‡ The thermodynamic water activity (a_w) describes the mass action effect of water on hydrolytic equilibria and also describes the partitioning of various water phases that can compete for water binding (ref. 1).

§ Polyacrylamide gel electrophoresis of CALB desorbed from the solid support exhibited a single band corresponding to the reported molecular weight of CALB (33 KDa) (ref. 6).

¶ (±)-2-Phenyl-4-benzyloxazol-5(4*H*)-one **1** (0.16 mmol) was placed in a 4 ml screw top vial together with the solvent, (either anhydrous or hydrated), butan-1-ol (0.24 mmol, 1.5 equiv.) CALB (40 mg) and Et_3N (14 mol%). The reaction vial was shaken at 250 rpm on a rotary shaker at 37 °C and the progress and ee (%) of the reaction were monitored by chiral HPLC (Chiralcel-OD, 250 × 4.6 mm, Mallinckrodt Baker, n-hexane–Pr^{i}OH (90:10 v/v), UV detection λ = 254 nm).

‖ *Candida antarctica* lipase B (CALB) was received as an immobilised preparation (Novozym 435, Boehringer Mannheim, Germany) and was dehydrated over P_2O_5 (at room temp.) for 2–3 days. Rehydration of dried lipase to the desired water activity (a_w) was carried out using saturated salt solutions (equilibration period 48–72 h). (±)-2-Phenyl-4-benzyloxazol-5(4*H*)-one **1** was stored over P_2O_5 at 0 °C; anhydrous solvents were stored over freshly reactivated 3 Å or 4 Å molecular sieves. The water content of dried solvents was measured using Karl Fischer water titration (ref. 15) and found to be <0.001 wt%. Solvents were hydrated separately from the enzyme using the same water equilibration procedure as described above, approximately 24 h before use.

** Control reactions showed that no detectable ester (as judged by HPLC) was formed in the absence of enzyme, either with or without Et_3N, over a 48 h analysis period.

†† Other organic bases give very similar results to Et_3N, *e.g.* DABCO and lutidine. Insoluble inorganic bases, *e.g.* $KHCO_3$ and K_2CO_3, had no effect and did not result in the high catalytic rate and enantioselectivity observed with the soluble organic bases.

‡‡ Electrospray ionisation mass spectrometry (ESI-MS) and atmospheric chemical ionisation (APCI) were performed on a Micromass Platform II spectrometer (cone voltage 20 V).

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Received in Liverpool, UK, 10th August 1998; 8/06332J